```
      ---  -----  -----------
? s trail
      S1   13644  TRAIL
? s mifepristone
      S2    6570  MIFEPRISTONE
? s s1 and s2
           13644  S1
            6570  S2
      S3      12  S1 AND S2
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S4       8  RD (unique items)
? t s4/4,k,ab/1-8

 4/4,K,AB/1     (Item 1 from file: 155)
FN- DIALOG(R)File 155:MEDLINE(R)|
CZ- (c) format only 2004 The Dialog Corp. All rts. reserv.|
12158605   PMID: 12492116
   Mifepristone pretreatment overcomes resistance of prostate cancer
cells to tumor necrosis factor alpha-related apoptosis-inducing ligand (
TRAIL).
  Eid Manal A; Lewis Ronald W; Kumar M Vijay
  Medical College of Georgia, Section of Urology, Veterans Administration
Medical Center, Augusta, Georgia 30912-4050, USA.
  Molecular cancer therapeutics (United States) Aug 2002, 1 (10)
 p831-40, ISSN 1535-7163 Journal Code: 101132535
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Subfile:  INDEX MEDICUS
  Examination of the effects of TRAIL (tumor necrosis factor
alpha-related apoptosis-inducing ligand) showed higher apoptotic response
in LNCaP C4-2, whereas LNCaP were resistant. However, treatment of LNCaP
with Mifepristone, an antiprogestin, before TRAIL induced
significant apoptosis, similar to the levels observed in LNCaP C4-2.
Experiments to determine the reasons for altered response of the cell lines
showed no significant differences in death/decoy receptors and caspase-8
activity. However, treatment induced increased truncation of Bid and
activation of caspases -9, -7, and -3 in LNCaP C4-2. Time course
experiments showed that caspase-8 was activated before the involvement of
mitochondrial pathway, and caspase-9 was responsible for activation of
caspases -7 and -3. Use of specific caspase inhibitors demonstrated the
presence of a short-loop feedback activation of Bid. Published reports
suggested that increased phosphorylation of Akt was responsible for
resistance of LNCaP to TRAIL. However, no significant differences
were noticed in the levels of phosphorylated Akt in TRAIL-resistant
LNCaP and TRAIL-sensitive LNCaP C4-2. On the basis of our results, it
is suggested that the differences in response of the two cell lines to
TRAIL is at the mitochondrial level.
  Tags: Human; Male
  Descriptors:  Hormone  Antagonists--pharmacology--PD;  *Membrane
Glycoproteins--metabolism--ME; *Mifepristone--pharmacology--PD; *Pros
tatic Neoplasms--drug therapy--DT; *Tumor Necrosis Factor--metabolism--ME;
Apoptosis; Blotting, Western; Carrier Proteins--metabolism--ME; Caspases
--metabolism--ME; Cytochrome c Group--metabolism--ME; Cytosol--metabolism
--ME;  Mitochondria--metabolism--ME;  Phosphorylation;  Proto-Oncogene
Proteins--metabolism--ME; Time Factors; Tumor Cells, Cultured
  CAS Registry No.: 0 (BID protein); 0 (Carrier Proteins); 0
 (Cytochrome c Group); 0 (Hormone Antagonists); 0 (Membrane
Glycoproteins); 0 (Proto-Oncogene Proteins); 0 (TNF-related
```

apoptosis-inducing ligand); 0 (Tumor Necrosis Factor); 0 (proto-oncogene protein akt); 84371-65-3 (Mifepristone)
Enzyme No.: EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (Caspases); EC 3.4.22.- (ICE-LAP6 protein); EC 3.4.22.- (caspase 7); EC 3.4.22.- (caspase 8)
Record Date Created: 20021220
Record Date Completed: 20030407

**Mifepristone** pretreatment overcomes resistance of prostate cancer cells to tumor necrosis factor alpha-related apoptosis-inducing ligand ( **TRAIL**).

Examination of the effects of **TRAIL** (tumor necrosis factor alpha-related apoptosis-inducing ligand) showed higher apoptotic response in LNCaP C4-2, whereas LNCaP were resistant. However, treatment of LNCaP with **Mifepristone**, an antiprogestin, before **TRAIL** induced significant apoptosis, similar to the levels observed in LNCaP C4-2. Experiments to determine...

... Published reports suggested that increased phosphorylation of Akt was responsible for resistance of LNCaP to **TRAIL**. However, no significant differences were noticed in the levels of phosphorylated Akt in **TRAIL** -resistant LNCaP and **TRAIL**-sensitive LNCaP C4-2. On the basis of our results, it is suggested that the differences in response of the two cell lines to **TRAIL** is at the mitochondrial level.

Descriptors: Hormone Antagonists--pharmacology--PD; *Membrane Glycoproteins--metabolism--ME; ***Mifepristone**--pharmacology--PD; *Prostatic Neoplasms--drug therapy--DT; *Tumor Necrosis Factor--metabolism--ME
...Chemical Name: Proto-Oncogene Proteins; TNF-related apoptosis-inducing ligand; Tumor Necrosis Factor; proto-oncogene protein akt; **Mifepristone**; CPP32 protein; Caspases; ICE-LAP6 protein; caspase 7; caspase 8

4/4,K,AB/2 (Item 2 from file: 155)
FN- DIALOG(R)File 155:MEDLINE(R)|

11476261 PMID: 11585752

Differential expression of members of the tumor necrosis factor alpha-related apoptosis-inducing ligand pathway in prostate cancer cells.

Sridhar S; Ali A A; Liang Y; El Etreby M F; Lewis R W; Kumar M V
Medical College of Georgia, Section of Urology, Augusta, Georgia 30912, USA.

Cancer research (United States) Oct 1 2001, 61 (19) p7179-83, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

Androgen ablation therapy induces apoptosis only in androgen-sensitive prostate cancer cells; therefore, other cytotoxic drugs are being used to induce apoptosis in androgen-refractory cells. **Mifepristone** , an antiprogestin used individually or together with the antiestrogen Tamoxifen, has been recommended for induction of cell death and treatment of several hormonal cancers. However, little is known about the mechanism of action of these drugs in prostate cancer. Therefore, we investigated the effect of **Mifepristone** on the tumor necrosis factor alpha-related apoptosis-inducing ligand (**TRAIL** ) pathway, a newly identified and very effective member of tumor necrosis factor-alpha family. **Mifepristone** and Tamoxifen induced significant expression of death receptors in prostate cancer cells in vitro and in xenografts. However, **Mifepristone** in combination with Tamoxifen did not increase prostate cancer cell death compared with their individual values. The involvement of the **TRAIL** pathway was further confirmed by the activation of

caspase-8 in **Mifepristone** -treated cells. This was followed by truncation of Bid, confirming that **Mifepristone** activates the **TRAIL** pathway. This knowledge is being used to design a combination treatment of **TRAIL** and **Mifepristone** to induce significant apoptosis in prostate cancer cells.

Tags: Human; Male

Descriptors: *Apoptosis--physiology--PH; *Membrane Glycoproteins --biosynthesis--BI; *Prostatic Neoplasms--metabolism--ME; *Receptors, Tumor Necrosis Factor--biosynthesis--BI; *Tumor Necrosis Factor--biosynthesis--BI ; Animals; Antineoplastic Agents, Hormonal--pharmacology--PD; Antineoplastic Combined Chemotherapy Protocols--pharmacology--PD; Apoptosis --drug effects--DE; Mice; Mice, Inbred BALB C; Mice, Nude; **Mifepristone**--pharmacology--PD; Prostatic Neoplasms--pathology--PA; Signal Transduction--drug effects--DE; Signal Transduction--physiology--PH ; Tamoxifen--pharmacology--PD; Tumor Cells, Cultured; Xenograft Model Antitumor Assays

CAS Registry No.: 0 (Antineoplastic Agents, Hormonal); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Membrane Glycoproteins); 0 (Receptors, Tumor Necrosis Factor); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor); 0 (death receptor-4); 0 (death receptor-5); 10540-29-1 (Tamoxifen); 84371-65-3 (Mifepristone)

Record Date Created: 20011004

Record Date Completed: 20011018

... cells; therefore, other cytotoxic drugs are being used to induce apoptosis in androgen-refractory cells. **Mifepristone** , an antiprogestin used individually or together with the antiestrogen Tamoxifen, has been recommended for induction...

... mechanism of action of these drugs in prostate cancer. Therefore, we investigated the effect of **Mifepristone** on the tumor necrosis factor alpha-related apoptosis-inducing ligand (**TRAIL** ) pathway, a newly identified and very effective member of tumor necrosis factor-alpha family. **Mifepristone** and Tamoxifen induced significant expression of death receptors in prostate cancer cells in vitro and in xenografts. However, **Mifepristone** in combination with Tamoxifen did not increase prostate cancer cell death compared with their individual values. The involvement of the **TRAIL** pathway was further confirmed by the activation of caspase-8 in **Mifepristone** -treated cells. This was followed by truncation of Bid, confirming that **Mifepristone** activates the **TRAIL** pathway. This knowledge is being used to design a combination treatment of **TRAIL** and **Mifepristone** to induce significant apoptosis in prostate cancer cells.

...; Chemotherapy Protocols--pharmacology--PD; Apoptosis--drug effects --DE; Mice; Mice, Inbred BALB C; Mice, Nude; **Mifepristone** --pharmacology--PD; Prostatic Neoplasms--pathology--PA; Signal Transduction --drug effects--DE; Signal Transduction--physiology--PH...

...Chemical Name: TNF-related apoptosis-inducing ligand; Tumor Necrosis Factor; death receptor-4; death receptor-5; Tamoxifen; **Mifepristone**

4/4,K,AB/3 (Item 3 from file: 155)



09376249 PMID: 1633899 Record Identifier: 074513; 00220446

Interruption of endometrial maturation without hormonal changes by an antiprogesterone during the first half of luteal phase of the menstrual cycle: a contraceptive potential.

Greene K E; Kettel L M; Yen S S

University of California-San Diego, School of Medicine, La Jolla.

Fertility and sterility (UNITED STATES) Aug 1992, 58 (2) p338-43, ISSN 0015-0282 Journal Code: 0372772

TJ: FERTILITY AND STERILITY.

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Other Citation Owner: PIP; POP
Abstract Source: PIP
Record type: Completed
Subfile: INDEX MEDICUS

OBJECTIVE: To examine hormonal and endometrial responses to intermittent low-dose RU486 administration in the luteal phase of the menstrual cycle. DESIGN: Prospective open trial in which subjects serve as their own controls. PATIENTS/PARTICIPANTS: Eight normal cycling women. INTERVENTIONS: RU486 (10 mg, orally) was administered 5 and 8 days after urinary luteinizing hormone (LH) surge of treatment cycle. MAIN OUTCOME MEASURES: Daily serum concentrations of LH, follicle-stimulating hormone, estradiol (E2), and progesterone (P) were determined in control, treatment, and recovery cycles (n = 5) or treatment and recovery cycles (n = 3). Changes in endometrial morphology and immunohistochemical staining for P receptor (PR) and E2 receptor (ER) were determined during control (or recovery) and treatment cycles. RESULTS: Cycle length and hormonal patterns were unaltered after treatment with RU486. As demonstrated by reduced stromal edema and delayed glandular development, endometrial dyssynchrony occurred in all eight treatment cycles. In addition, seven of eight treatment cycle endometria demonstrated a decrease in PR staining without consistent change in ER staining. CONCLUSIONS: Two low doses of RU486 given 72 hours apart during the luteal phase of the cycle disrupted ongoing endometrial maturation without altering the hormonal and time course of the menstrual cycle. This study provides a basis for the development of a novel form of luteal contraception.

This study sought to examine hormonal and endometrial responses to intermittent low-dose RU486 administration in the luteal phase of the menstrual cycle. 8 normally cycling women participated in this prospective open **trail** in which the subjects served as their own controls. RU486 (10 mg, orally) was administered 5 and 8 days after urinary luteinizing hormone (LH) surge of treatment cycle. Daily serum concentrations of LH, follicle stimulating hormone, estradiol (E2), and progesterone (P) were determined in control, treatment, and recovery cycles (n=5) or treatment and recovery cycles (n=3). Changes in endometrial morphology and immunohistochemical staining for P receptor (PR) and E2 receptor (ER) were determined during control (or recovery) and treatment cycles. Cycle length and hormonal patterns were unaltered after treatment with RU486. As demonstrated by reduced stromal edema and delayed glandular development, endometrial dyssynchrony occurred in all 8 treatment cycles. In addition, 7 of 8 treatment cycle endometria demonstrated a decrease in PR staining without consistent change in Er staining. The authors conclude that 2 low doses of RU486 given 72 hours apart during the luteal phase of the cycle disrupt ongoing endometrial maturation without altering the hormonal and time course of the menstrual cycle. This study provides a basis for the development of a novel form of luteal contraception. author's modified

Tags: Female; Human; Support, Non-U.S. Gov't

Descriptors: Contraceptives, Oral--pharmacology--PD; *Endometrium --physiology--PH; *Luteal Phase; ***Mifepristone**--pharmacology--PD; Adult; Endometrium--anatomy and histology--AH; Endometrium--drug effects --DE; Estradiol--blood--BL; Follicle Stimulating Hormone--blood--BL; Immunoenzyme Techniques; Luteinizing Hormone--blood--BL; **Mifepristone** --administration and dosage--AD; Progesterone--blood--BL; Prospective Studies; Receptors, Estradiol; Receptors, Progesterone--metabolism--ME

CAS Registry No.: 0 (Contraceptives, Oral); 0 (Receptors, Estradiol); 0 (Receptors, Progesterone); 50-28-2 (Estradiol); 57-83-0 (Progesterone); 84371-65-3 (Mifepristone); 9002-67-9 (Luteinizing Hormone); 9002-68-0 (Follicle Stimulating Hormone)

Identifiers: *Americas; *Biology; *California; *Clinical Research; *Clinical Trials; *Contraception; *Contraception Research; *Developed Countries; *Endocrine System; *Endometrial Effects; *Endometrium; *Examinations And Diagnoses; *Family Planning; *Follicle Stimulating

Hormone--analysis; *Genitalia; *Genitalia, Female; *Gonadotropins; *Gonadotropins, Pituitary; *Histology; *Hormone Antagonists; *Hormone Receptors; *Hormones; *Laboratory Examinations And Diagnoses; *Luteinizing Hormone--analysis; *Membrane Proteins; *Menstrual Cycle; *Menstruation; *North America; *Northern America; *Physiology; *Progestational Hormones; *Progesterone--analysis; *Prospective Studies; *Reproduction; *Research Methodology; *Ru-486; *Studies; *United States; *Urogenital System; *Uterus
Record Date Created: 19920825
Record Date Completed: 19920825

... luteal phase of the menstrual cycle. 8 normally cycling women participated in this prospective open **trail** in which the subjects served as their own controls. RU486 (10 mg, orally) was administered...
Descriptors: Contraceptives, Oral--pharmacology--PD; *Endometrium --physiology--PH; *Luteal Phase; ***Mifepristone**--pharmacology--PD...; DE; Estradiol--blood--BL; Follicle Stimulating Hormone--blood--BL; Immunoenzyme Techniques; Luteinizing Hormone--blood--BL; **Mifepristone** --administration and dosage--AD; Progesterone--blood--BL; Prospective Studies; Receptors, Estradiol; Receptors, Progesterone--metabolism--ME
Chemical Name: Contraceptives, Oral; Receptors, Estradiol; Receptors, Progesterone; Estradiol; Progesterone; **Mifepristone**; Luteinizing Hormone; Follicle Stimulating Hormone

4/4,K,AB/4 (Item 4 from file: 155)
FN- DIALOG(R)File 155:MEDLINE(R)|

06440688 PMID: 12285435 Record Identifier: 073271; 00218427
Abortion. Is RU 486/PG in its current form likely to be appropriate for women in Bangladesh?
Kabir S; Germain A
Newsletter (Women's Global Network on Reproductive Rights) (NETHERLANDS)
Jan-Mar 1992, (38) p39-45, Journal Code: 101084378
TJ: WOMEN'S GLOBAL NETWORK FOR REPRODUCTIVE RIGHTS NEWSLETTER
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: PIP
Other Citation Owner: PIP; POP
Abstract Source: PIP
Record type: Completed
In 1991 in Bangladesh, women's health advocates presented a paper at the International Symposium on Antiprogestins on the pros and cons of a clinical trial of RU-486 and a prostaglandin (RU-486/PG) in Bangladesh where women now depend on menstrual regulation (MR). Even though RU-486/PG does not depend on a transcervical procedure as does MR, it requires a pelvic examination to determine gestation and completeness of abortion. Bangladeshi women consider it an invasive procedure. Thus, the often proclaimed benefit of noninvasiveness does not apply. Further, pelvic exams carry the risk of infection. Other sources of infection with RU-486/PG are insertion of PG vaginal suppository, retained conceptus, and management of blood loss. There is a sizable risk of infection in a not tightly controlled trial because women may not recognize incomplete abortion. MR also has similar risk of infection, especially the more serious risk of upper genital tract infection. RU-486/PG is most effective within 7-8 weeks after the last menstrual period. Yet, most women in rural Bangladesh present for MR at or after 8 weeks, and clinics countrywide have turned away 20-40% of women because they present no earlier than 10 weeks. Like MR, RU-486/PG does not allow Bangladeshi women any privacy because they must go to the clinic 3 times and both family and community know when they are bleeding. A clinical trial would determine whether Bangladeshi women would have the sense of control as expressed by French women. RU-486/PG would not necessarily lower costs for the health system or women. Further, it would not prevent deaths from septic abortions. The advocates recommended a **trail** in Bangladesh, if certain conditions were met

such as involvement of women's health advocates in every stage of the trial and use of only the highest possible quality service providers. It should only occur in carefully controlled clinical situations.
Tags: Pregnancy
Descriptors: Abortifacient Agents; *Abortion, Induced; *Clinical Trials; *Evaluation Studies; *Gestational Age; *Menstruation; ***Mifepristone**; *Patient Acceptance of Health Care; *Politics; *Prostaglandins, Synthetic; *Public Opinion; *Quality of Health Care; *Women; Asia; Bangladesh; Biology ; Contraception; Contraception Behavior; Contraceptives, Postcoital; Developing Countries; Endocrine System; Family Planning Services; Fetus; Health Services Research; Hormone Antagonists; Hormones; Organization and Administration; Physiology; Program Evaluation; Prostaglandins; Reproduction; Research
CAS Registry No.: 0 (Abortifacient Agents); 0 (Contraceptives, Postcoital); 0 (Hormone Antagonists); 0 (Hormones); 0 (Prostaglandins) ; 0 (Prostaglandins, Synthetic); 84371-65-3 (Mifepristone)
Identifiers: *Abortifacient Agents--beneficial effects; *Abortifacient Agents--cost; *Abortifacient Agents--side effects; *Abortion, Drug Induced; *Abortion, Induced; *Asia; *Bangladesh; *Biology; *Clinical Research; *Clinical Trials; *Contraception; *Contraceptive Usage; *Critique; *Developing Countries; *Endocrine System; *Family Planning; *Fertility Control, Postcoital; *Fertility Control, Postconception; *Fetus; *Gestational Age; *Health Services Evaluation; *Hormone Antagonists; *Hormones; *Interest Groups; *Menstrual Regulation; *Method Acceptability; *Organization And Administration; *Physiology; *Political Factors; *Pregnancy; *Pro-choice Groups; *Program Evaluation; *Programs; *Prostaglandins; *Prostaglandins, Synthetic; *Quality Of Health Care; *Reproduction; *Research Methodology; *Ru-486; *Southern Asia; *Women's Groups
Record Date Created: 19930804
Record Date Completed: 19930804

... or women. Further, it would not prevent deaths from septic abortions. The advocates recommended a **trail** in Bangladesh, if certain conditions were met such as involvement of women's health advocates...
Descriptors: Abortifacient Agents; *Abortion, Induced; *Clinical Trials; *Evaluation Studies; *Gestational Age; *Menstruation; ***Mifepristone**; *Patient Acceptance of Health Care; *Politics; *Prostaglandins, Synthetic; *Public Opinion; *Quality of Health Care; *Women
Chemical Name: Abortifacient Agents; Contraceptives, Postcoital; Hormone Antagonists; Hormones; Prostaglandins; Prostaglandins, Synthetic; **Mifepristone**

4/4,K,AB/5 (Item 5 from file: 155)
FN- DIALOG(R)File 155:MEDLINE(R)|

06440187 PMID: 12283629 Record Identifier: 064799; 00200583
Abortion induced by **mifepristone** and sulprostone combination: attempting analgesia with acetominophen or dipropyline]
Interruptions volontaires de grossesse induites par l'association **mifepristone** -sulprostone: essai d'antalgie par le paracetamol ou la dipropyline.
Weber B; Fontan J E; Scheller E; Debu E; Dufour B; Majorel P; Langlade A
Contraception, fertilite, sexualite (FRANCE) Dec 1990, 18 (12) p1073-6, ISSN 0301-861X Journal Code: 0411244
TJ: CONTRACEPTION, FERTILITE, SEXUALITE
Document type: Journal Article ; English Abstract
Languages: FRENCH
Main Citation Owner: PIP
Other Citation Owner: PIP; POP
Abstract Source: PIP
Record type: Completed
45 women undergoing 1st trimester abortions induced by RU-486 were

divided into 3 groups for a double-blind randomized vs. placebo **trail** of analgesia following sulprostone administration. 600 mg of RU-486 was administered orally 36-48 hours before admission to the hospital. After admission, 10 women received 600 mg of acetaminophen, 14 received 80 mg of dipropyline, and 14 received a placebo. 500 mcg of sulprostone was injected about 30 minutes later. The study excluded method failures, expulsions occurring before hospital admission, deviations from the protocol, and delays to expulsion greater than 8 hours. There was no significant difference between the 3 groups in maximal pain, but the placebo group appeared to experience less discomfort than the other two. The delay to expulsion was significantly longer in the acetaminophen group than in the other two. The relatively lower amount of pain in the placebo group was probably due to the reduced proportion of nulliparas in it compared to the other 2 groups. 6 women in the acetaminophen group, 9 in the dipropyline group, and only 5 in the placebo group were nulliparas. Comparing nulliparas with mothers within groups, the maximal pain was significantly less intense among mothers than among nulliparas in the placebo group and to a lesser extent in the dipropyline group but not in the acetaminophen group. Based on these results it is recommended that a systematic study be made of analgesia for RU-486 and sulprostone-induced abortions. An antispasmodic effect on the cervical fibers should be sought more than analgesia per se.

Tags: Pregnancy

Descriptors: Abortion, Induced; *Analgesia; *Double-Blind Method; *Mifepristone; *Pain; *Pregnancy Trimester, First; *Prostaglandins, Synthetic; *Time Factors; Biology; Demography; Developed Countries; Disease ; Endocrine System; Europe; Family Planning Services; France; Hormone Antagonists; Hormones; Physiology; Population; Population Dynamics; Prostaglandins; Reproduction; Research; Signs and Symptoms; Therapeutics

CAS Registry No.: 0 (Hormone Antagonists); 0 (Hormones); 0 (Prostaglandins); 0 (Prostaglandins, Synthetic); 84371-65-3 (Mifepristone)

Identifiers: *Abortion, Induced; *Analgesia; *Biology; *Demographic Factors; *Developed Countries; *Diseases; *Double-blind Studies; *Endocrine System; *Europe; *Family Planning; *Fertility Control, Postconception; *France; *Hormone Antagonists; *Hormones; *Mediterranean Countries; *Pain; *Physiology; *Population; *Population Dynamics; *Pregnancy; *Pregnancy, First Trimester; *Prostaglandins; *Prostaglandins, Synthetic; *Reproduction ; *Research Methodology; *Ru-486--administraction and dosage; *Signs And Symptoms; *Studies; *Time Factors; *Treatment; *Western Europe

Record Date Created: 19910603

Record Date Completed: 19910603

Abortion induced by **mifepristone** and sulprostone combination: attempting analgesia with acetominophen or dipropyline]

Interruptions volontaires de grossesse induites par l'association **mifepristone** -sulprostone: essai d'antalgie par le paracetamol ou la dipropyline.

...by RU-486 were divided into 3 groups for a double-blind randomized vs. placebo **trail** of analgesia following sulprostone administration. 600 mg of RU-486 was administered orally 36-48...

Descriptors: Abortion, Induced; *Analgesia; *Double-Blind Method; *Mifepristone; *Pain; *Pregnancy Trimester, First; *Prostaglandins, Synthetic; *Time Factors

Chemical Name: Hormone Antagonists; Hormones; Prostaglandins; Prostaglandins, Synthetic; **Mifepristone**

4/4,K,AB/6 (Item 1 from file: 55)

FN- DIALOG(R)File 55:Biosis Previews(R)|



0013961046 BIOSIS NO.: 200200554557

Induction of apoptosis as a treatment option for prostate cancer

AUTHOR: Kumar M V (Reprint); Eid M A (Reprint); Liang Y (Reprint); Lewis R

W (Reprint)
AUTHOR ADDRESS: Section of Urology, Medical College of Georgia, Augusta, GA, USA**USA
JOURNAL: International Journal of Cancer Supplement (13): p341 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 18th UICC International Cancer Congress Oslo, Norway June 30-July 05, 2002; 20020630
ISSN: 0898-6924
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 84371-65-3: **mifepristone**
DESCRIPTORS:
MAJOR CONCEPTS: Pharmacology; Reproductive System--Reproduction; Tumor Biology; Urinary System--Chemical Coordination and Homeostasis
DISEASES: prostate cancer--neoplastic disease, reproductive system disease/male, urologic disease
MESH TERMS: Prostatic Neoplasms (MeSH)
CHEMICALS & BIOCHEMICALS: NF-kappa-B {nuclear factor-kappa-B}--expression, regulation; TNF-alpha related apoptosis inducing ligand {**TRAIL**}--antineoplastic-drug, pharmacodynamics; androgen--androgen-drug, antineoplastic-drug; death receptor-4 {DR4}--expression, regulation; death receptor-5 {DR5}--expression, regulation; **mifepristone**--antineoplastic-drug, pharmacodynamics
MISCELLANEOUS TERMS: tumor response; Meeting Abstract; Meeting Abstract
CONCEPT CODES:
00520 General biology - Symposia, transactions and proceedings
10064 Biochemistry studies - Proteins, peptides and amino acids
12512 Pathology - Therapy
15504 Urinary system - Physiology and biochemistry
15506 Urinary system - Pathology
16504 Reproductive system - Physiology and biochemistry
16506 Reproductive system - Pathology
22002 Pharmacology - General
22016 Pharmacology - Endocrine
24004 Neoplasms - Pathology, clinical aspects and systemic effects
24008 Neoplasms - Therapeutic agents and therapy

...REGISTRY NUMBERS: **mifepristone**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...TNF-alpha related apoptosis inducing ligand {**TRAIL**}--...

...**mifepristone**--

4/4,K,AB/7 (Item 2 from file: 55)
FN- DIALOG(R)File 55:Biosis Previews(R)|
CZ- (c) 2004 BIOSIS. All rts. reserv.|
0013815636 BIOSIS NO.: 200200409147
Pre-treatment with **mifepristone** sensitizes resistant prostate cancer cells to **TRAIL**
AUTHOR: Eid Manal A (Reprint); Lewis Ronald W (Reprint); Kumar M Vijay (Reprint)
AUTHOR ADDRESS: Medical College of Georgia, Augusta, GA, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43 p579 March, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation

LANGUAGE: English
REGISTRY NUMBERS: 189258-14-8: caspase 7; 179241-78-2: caspase 8; 180189-96-2: caspase 9; 84371-65-3: **mifepristone**
DESCRIPTORS:
MAJOR CONCEPTS: Pharmacology; Reproductive System--Reproduction; Tumor Biology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: LNCaP cell line (Hominidae)--apoptosis, human prostate adenocarcinoma cells; PCa cell line (Hominidae)--human prostate cancer cells
ORGANISMS: PARTS ETC: mitochondria; prostate--excretory system, reproductive system
COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates
DISEASES: prostate cancer--neoplastic disease, reproductive system disease/male, urologic disease
MESH TERMS: Prostatic Neoplasms (MeSH)
CHEMICALS & BIOCHEMICALS: Bid--regulation; androgen; caspase 7--regulation; caspase 8--regulation; caspase 9; death receptor--regulation; downstream activator--activation; **mifepristone**--antineoplastic-drug; tumor necrosis factor-alpha related apoptosis ligand {**TRAIL**}--antineoplastic-drug
MISCELLANEOUS TERMS: mitochondrial apoptotic pathway; Meeting Abstract; Meeting Abstract
CONCEPT CODES:
00520 General biology - Symposia, transactions and proceedings
02508 Cytology - Human
12512 Pathology - Therapy
15504 Urinary system - Physiology and biochemistry
15506 Urinary system - Pathology
16504 Reproductive system - Physiology and biochemistry
16506 Reproductive system - Pathology
22002 Pharmacology - General
22005 Pharmacology - Clinical pharmacology
24004 Neoplasms - Pathology, clinical aspects and systemic effects
24008 Neoplasms - Therapeutic agents and therapy
BIOSYSTEMATIC CODES:
86215 Hominidae

Pre-treatment with **mifepristone** sensitizes resistant prostate cancer cells to **TRAIL**
...REGISTRY NUMBERS: **mifepristone**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...**mifepristone**--...

...tumor necrosis factor-alpha related apoptosis ligand {**TRAIL**}--

4/4,K,AB/8 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent


Dialog Acc No: 10171921 IFI Acc No: 2002-0115613 IFI Acc No: 2002-0029792
Document Type: C
TREATMENT OF PROSTATE CANCER; INDUCING CELL DEATH BY TREATING WITH TUMOR NECROSIS FACTOR ALPHA-RELATED APOPTOSIS INDUCING LIGAND (**TRAIL**) AND, OPTIONALLY AN ANTIPROGESTIN, E.G., **MIFEPRISTONE**
Document Type: Utility
Document Type: Patent Application-First Publication
Inventors: Kumar M Vijay (US)
Assignee: Unassigned Or Assigned To Individual
Assignee Code: 68000
Publication (No,Date), Applic (No,Date):

US 20020115613 20020822 US 200277435 20020215
Publication Kind: A1
Priority Applic(No,Date): US 200277435 20020215
Provisional Applic(No,Date): US 60-269698 20010216

Abstract: The present invention provides methods and compositions for treating cancer, and even more preferably, prostate cancer. In one aspect, the present invention comprises a method for inducing cell death in cancer cells comprising treating at least a portion of the cancer cells with an effective amount of **TRAIL** and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a portion of the treated cancer cells. In another aspect, the present invention comprises a composition for treating cancer by inducing cell death in cancer cells comprising a pharmaceutical composition comprising an effective amount of **TRAIL** and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a portion of the cancer cells exposed to the composition. In an embodiment, the antiprogestin is **Mifepristone**.

...INDUCING CELL DEATH BY TREATING WITH TUMOR NECROSIS FACTOR ALPHA-RELATED APOPTOSIS INDUCING LIGAND (**TRAIL**) AND, OPTIONALLY AN ANTIPROGESTIN, E.G., **MIFEPRISTONE**

Abstract: ...comprising treating at least a portion of the cancer cells with an effective amount of **TRAIL** and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a...

...inducing cell death in cancer cells comprising a pharmaceutical composition comprising an effective amount of **TRAIL** and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a portion of the cancer cells exposed to the composition. In an embodiment, the antiprogestin is **Mifepristone**.

Exemplary Claim: ...death in cancer cells, the method comprising treating cancer cells with an effective amount of **TRAIL** sufficient to induce apoptosis in at least a portion of the treated cancer cells.
Non-exemplary Claims: ...death in cancer cells, the method comprising treating cancer cells with an effective amount of **TRAIL** and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a...

...3. The method of claim 2, wherein the antiprogestin comprises **Mifepristone**.
...

...the method comprising treating cancer cells with a pharmaceutical composition comprising an effective amount of **TRAIL** and an effective amount of **Mifepristone** sufficient to induce apoptosis in at least a portion of the treated cancer cells...

...5. The method of claim 4, wherein the cancer cells are treated with **Mifepristone** prior to being treated with **TRAIL**.
...
...6. The method of claim 4, wherein the cancer cells are treated with **Mifepristone** and **TRAIL** concurrently...

...7. The method of claim 4, wherein the dose of **TRAIL** in said pharmaceutical composition results in a local concentration of **TRAIL** at the tumor which ranges from 1 to 1,000 ng/ml...

...8. The method of claim 4, wherein the dose of **TRAIL** in said pharmaceutical composition results in a local concentration of **TRAIL** at the tumor which ranges from 200 to 600 ng/ml...

...9. The method of claim 4, wherein the dose of **TRAIL** in said pharmaceutical composition results in a local concentration of **TRAIL** at the tumor which ranges from 350 to 450 ng/ml...

...10. The method of claim 4, wherein the dose of **Mifepristone** in said pharmaceutical composition results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 1,000 mu M...

...11. The method of claim 4, wherein the dose of **Mifepristone** in said pharmaceutical composition results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 100 mu M...
...12. The method of claim 4, wherein the dose of **Mifepristone** in said pharmaceutical composition results in a local concentration of **Mifepristone** at the tumor which ranges from 5 to 20 mu M...16. The method of claim 4, wherein the treatment of cancer cells with **TRAIL** and **Mifepristone** is associated with an increase in at least one death receptor in at least a...

...18. The method of claim 4, wherein the treatment of cancer cells with **TRAIL** and **Mifepristone** is associated with an increase in activated caspase enzymes...

...20. The method of claim 4, wherein the treatment of cancer cells with **TRAIL** and **Mifepristone** is associated with an increase in truncated BID protein (tBid) in at least a portion...

...21. The method of claim 4, wherein the treatment of cancer cells with **TRAIL** and **Mifepristone** is associated with a reduction in mitochondrial function...

...22. The method of claim 4, wherein the treatment of cancer cells with **TRAIL** and **Mifepristone** results in an increase in apoptosome formation in at least a portion of the treated...
...for treating cancer by inducing cell death in cancer cells comprising an effective amount of **TRAIL** in a pharmaceutical carrier, wherein an effective amount comprises sufficient **TRAIL** to induce apoptosis in at least a portion of said cancer cells exposed to said...for treating cancer by inducing cell death in cancer cells comprising an effective amount of **TRAIL** and an antiprogestin in a pharmaceutical carrier, wherein an effective amount comprises sufficient **TRAIL** and antiprogestin to induce apoptosis in at least a portion of said cancer cells exposed...

...29. The composition of claim 28, wherein the antiprogestin comprises **Mifepristone**.
...

...for treating cancer by inducing cell death in cancer cells comprising an effective amount of **TRAIL** and **Mifepristone** in a pharmaceutical carrier, wherein an effective amount comprises sufficient **TRAIL** and **Mifepristone** to induce apoptosis in at least a portion of said cancer cells exposed to said...

...31. The composition of claim 30, wherein said **Mifepristone** and said **TRAIL** are packaged in such a manner that said **Mifepristone** is at least partially released for application to the cancer prior to the release of said **TRAIL**.
...

...32. The composition of claim 30, wherein said **Mifepristone** and said **TRAIL** are packaged in such a manner so as to be released substantially simultaneously...

...33. The composition of claim 30, wherein the dose of **TRAIL** results

in a local concentration of **TRAIL** at the tumor which ranges from 1 to 1,000 ng/ml...

...34. The composition of claim 30, wherein the dose of **TRAIL** results in a local concentration of **TRAIL** at the tumor which ranges from 200 to 600 ng/ml...

...35. The composition of claim 30, wherein the dose of **TRAIL** results in a local concentration of **TRAIL** at the tumor which ranges from 350 to 450 ng/ml...

...36. The composition of claim 30, wherein the dose of **Mifepristone** results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 1,000 mu M...

...37. The composition of claim 30, wherein the dose of **Mifepristone** results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 100 mu M...

...38. The composition of claim 30, wherein the dose of **Mifepristone** results in a local concentration of **Mifepristone** at the tumor which ranges from 5 to 20 mu M...42. A kit for pharmaceutical treatment of cancer comprising: (a) a pharmacologically effective amount of **TRAIL** packaged in a sterile container; (b) a pharmacologically effective amount of an antiprogestin packaged in...

...at least one aliquot of a pharmaceutical carrier; and (d) instructions for application of said **TRAIL** and said antiprogestin to a patient having cancer...

...43. The kit of claim 42, wherein said antiprogestin comprises **Mifepristone**.

?

9155277 Genuine Article#: 373TQ Number of References: 45
Title: Induction of **tumor**-selective apoptosis by **TRAIL**: A new road for oncology? (ABSTRACT AVAILABLE)
Author(s): vonOphoven A (REPRINT)
Corporate Source: UNIV MUNSTER,KLIN & POLIKLIN UROL, ALBERT SCHWEITZER STR 33/D-48129 MUNSTER//GERMANY/ (REPRINT)
Journal: AKTUELLE UROLOGIE, **2000**, V31, N6 (OCT), P347-352
ISSN: 0001-7868 Publication date: 20001000
Publisher: GEORG THIEME VERLAG KG, RUDIGERSTR 14, D-70469 STUTTGART, GERMANY
Language: German Document Type: REVIEW
Abstract: Purpose: The physiological significance of **tumor necrosis** factor (TNF)-related apoptosis-inducing ligand ( **TRAIL**) in apoptosis is presented herein. Its potential application as a therapeutic agent in urologic oncology is discussed.

Materials and Methods: The pertinent literature on the molecular biology of **TRAIL**, its receptors and future potential for therapy in urologic oncology is reviewed and duscussed.

Results: The recent discovery and characterization of **TRAIL** has led to further insight into the apoptotic process. Based on preceding in vitro studies, the first in vivo study using **TRAIL** was conducted and published in 1999. Systemic application of **TRAIL** in SCID mice resulted in **tumor** regression of subcutaneously implanted mammary and colon **cancer**. Several groups are loking into **TRAIL** sensitivity to prostate and renal **cancer** cellines. Recent in vitro data showed a significant increase of apoptotic cell death rate following the **combined** application of **TRAIL** and chemotherapeutics.

Conclusions: In the future, **TRAIL** may be used in **combination** with other immunotherapies or gene therapies providing a synergistic effect or enhancing the

Molecular determinants of response to **TRAIL combined** with chemotherapy in killing of normal and **cancer** cells

AUTHOR: Kim K H; El-Deiry W S
AUTHOR ADDRESS: Howard Hughes Med. Inst., U. Penn., Philadelphia, PA 19104, USA**USA

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40 p486 March, 1999 **1999**
MEDIUM: print
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999; 19990410
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

**Tumor necrosis** factor-related apoptosis-inducing ligand's antitumor activity in vivo is enhanced by the chemotherapeutic agent CPT-11

AUTHOR: Gliniak Brian (Reprint); Le Tiep
AUTHOR ADDRESS: Department of Molecular Immunology, Immunex Corp., 51 University Street, Seattle, WA, 98101, USA**USA

JOURNAL: Cancer Research 59 (24): p6153-6158 Dec. 15, 1999 **1999**
MEDIUM: print
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

in vivo come in vitro 10/01/04

ABSTRACT: **Tumor necrosis** factor-related apoptosis-inducing ligand (**TRAIL**) can induce apoptosis in a wide variety of transformed human cells in vitro. In this study, the antitumor activity of recombinant **TRAIL** was analyzed in mice bearing human colon carcinoma tumors. We found that these tumors displayed a differential sensitivity to **TRAIL** in vivo that paralleled their susceptibility to **TRAIL**-induced apoptosis in vitro. Treatment of **TRAIL**-sensitive tumors 3 days after **tumor** challenge resulted in a dose-dependent inhibition of growth and the elimination of tumors in many mice. Colon carcinoma cell lines could be further sensitized to **TRAIL**-induced apoptosis in vitro by the addition of the chemotherapeutic agent camptothecin. Moreover, the **combination** of **TRAIL** and CPT-11, a water-soluble analogue of camptothecin, greatly enhanced the antitumor activity of **TRAIL** in vivo. **TRAIL** plus CPT-11 treatment of both 3- and 10-day established **TRAIL**-sensitive tumors resulted in both a significant inhibition of **tumor** growth and a high proportion of complete **tumor** regressions. Treatment of **TRAIL**-resistant tumors with **TRAIL** and CPT-11 dramatically slowed **tumor** growth and induced a transient **tumor** regression.

Synergistic effect of retinoids on TNF-related apoptosis-inducing ligand ( **TRAIL**)-induced apoptosis in human T cell leukemia lines
AUTHOR: Kato Kazunori (Reprint); Takaue Yoichi; Wakasugi Hiro (Reprint)
AUTHOR ADDRESS: Pharmacology Division, National Cancer Center Research Institute, Chuo-ku, Tokyo, Japan**Japan
JOURNAL: Blood 96 (11 Part 2): p145b November 16, 2000 **2000**
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000; 20001201
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Retinoids including All-trans retinoic acid (ATRA) and 9-cis retinoic acid (9-cis-RA) exert antitumoral effects in various **malignancies** and inhibit cell growth in cell lines derived from lung carcinoma, ovarian carcinoma, breast **cancer**, leukemia and lymphoma. Retinoids were reported to down-regulate the anti-apoptotic protein bcl-2 and to increase chemotherapy-induced cell death in acute promyelocytic leukemia (APL) or acute myelogenous leukemia (AML) lines. However, acute lymphoid leukemia (ALL) is resistant to ATRA-mediated cell growth inhibition or apoptosis. Recent studies have revealed that TNF-related apoptosis-inducing factor (**TRAIL**) is capable of inducing apoptosis in a variety of tumors, but not in normal tissues. In this study, we examined whether retinoids could potentiate **TRAIL** -induced apoptosis in various human lymphoblastic leukemia cell lines. Recombinant soluble **TRAIL**-induced apoptosis in 7 human lymphoid leukemia lines was assessed by flow cytometry using 3, 3'-dihexyloxacarbocyanine iodine (DiOC6) and propidium iodide (PI). We found that pretreatment with retinoids synergistically enhanced **TRAIL**-induced apoptosis of 3 leukemia lines in a dose (0.1 nM to 1 uM) and time (6 to 48 h) dependent manner. Retinoids had no effect themselves on cell viability and did not increase expression of death receptors, such as **TRAIL**-R1, -R2, TNF-R1 and Fas. The active form of caspase-3 in leukemia lines was significantly up-regulated by the **combination** with retinoids and **TRAIL** than in treatment with retinoids or **TRAIL** alone. In addition, exposure of these cell lines to retinoids resulted in enhancement of anti-Fas mAb- or TNFalpha-mediated cytotoxicity. Furthermore, leukemia lines pretreated with retinoids were susceptible to IL-2-activated killer cells that expressed **TRAIL** on the cell surface. Collectively, these results may provide a basis for a therapeutic strategy that **combines** retinoids and **TRAIL** treatment against human lymphoblastic leukemia.

Synergistic effect of retinoids on TNF-related apoptosis-inducing ligand ( **TRAIL**)-induced apoptosis in human T cell leukemia lines
**2000**

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...cell growth inhibition or apoptosis. Recent studies have revealed that TNF-related apoptosis-inducing factor (**TRAIL**) is capable of inducing apoptosis in a variety of tumors, but not in normal tissues. In this study, we examined whether retinoids could potentiate **TRAIL** -induced apoptosis in various human lymphoblastic leukemia cell lin

Increased expression of death receptors 4 and 5 synergizes the apoptosis response to **combined** treatment with etoposide and **TRAIL**.

Gibson S B; Oyer R; Spalding A C; Anderson S M; Johnson G L

Program in Molecular Signal Transduction, Division of Basic Sciences, National Jewish Medical and Research Center, Denver, Colorado 80206, USA.

Molecular and cellular biology (UNITED STATES) Jan **2000**, 20 (1) p205-12, ISSN 0270-7306 Journal Code: 8109087

Contract/Grant No.: DK37871; DK; NIDDK; DK48845; DK; NIDDK; GM303024; GM; NIGMS; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Chemotherapeutic genotoxins induce apoptosis in epithelial-cell-derived **cancer** cells. The death receptor ligand **TRAIL** also induces apoptosis in epithelial-cell-derived **cancer** cells but generally fails to induce apoptosis in nontransformed cells. We show here that the treatment of four different epithelial cell lines with the topoisomerase II inhibitor etoposide in **combination** with **TRAIL** (**tumor necrosis** factor [TNF]-related apoptosis-inducing ligand) induces a synergistic apoptotic response. The mechanism of the synergistic effect results from the etoposide-mediated increase in the expression of the death receptors 4 (DR4) and 5 (DR5). Inhibition of NF-kappaB activation by expression of kinase-inactive MEK kinase 1(MEKK1) or dominant-negative IkappaB (DeltaIkappaB) blocked the increase in DR4 and DR5 expression following etoposide treatment. Addition of a soluble decoy DR4 fusion protein (DR4:Fc) to cell cultures reduced the amount of etoposide-induced apoptosis in a dose-dependent manner. The addition of a soluble TNF decoy receptor (TNFR:Fc) was without effect, demonstrating the specificity of DR4 binding ligands in the etoposide-induced apoptosis response. Thus, genotoxin treatment in **combination** with **TRAIL** is an effective inducer of epithelial-cell-derived **tumor** cell apoptosis relative to

17/3,K,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


10585180 PMID: 10690508

Molecular determinants of response to **TRAIL** in killing of normal and **cancer** cells.

Kim K; Fisher M J; Xu S Q; el-Deiry W S

Howard Hughes Medical Institute, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.

Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Feb **2000**, 6 (2) p335-46, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA75138-01; CA; NCI; CA75454-01; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The **tumor necrosis** factor-related apoptosis-inducing ligand ( **TRAIL** or Apo2L) is a potent inducer of death of **cancer** but not normal cells, which suggests its potential use as a **tumor**-specific antineoplastic agent. **TRAIL** binds to the proapoptotic death receptors DR4 and the p53-regulated proapoptotic KILLER/DR5 as well as to the decoy receptors TRID and TRUNDD. In the present studies, we identified a subgroup of **TRAIL**-resistant **cancer** cell lines characterized by low or absent basal DR4 or high expression of the caspase activation inhibitor FLIP. Four of five **TRAIL**-sensitive cell lines expressed high levels of DR4 mRNA and protein, whereas six of six **TRAIL**-resistant cell lines expressed low or undetectable levels of DR4 (chi 2; $P < 0.01$). FLIP expression appeared elevated in five of six (83%) **TRAIL**-resistant cell lines and only one of five (20%) **TRAIL**-sensitive cells (chi 2; $P < 0.05$). Two **TRAIL**-resistant lines that expressed DR4 contained an A-to-G alteration in the death domain encoding arginine instead of lysine at codon 441. The K441R polymorphism is present in 20% of the normal population and can inhibit DR4-mediated cell killing in a dominant-negative fashion. The expression level of KILLER/DR5, TRID, TRUNDD or TRID, and TRUNDD did not correlate with **TRAIL** sensitivity ($P > 0.05$). These results suggest that the major determinants for **TRAIL** sensitivity may be the expression level of DR4 and FLIP. **TRAIL**-resistant cells became susceptible to **TRAIL** -mediated apoptosis in the presence of doxorubicin. In **TRAIL** -sensitive cells, caspases 8, 9, and 3 were activated after **TRAIL** treatment, but in **TRAIL**-resistant cells, they were activated only by the **combination** of **TRAIL** and doxorubicin. Our results suggest: (a) evaluation of **tumor** DR4 and FLIP expression and host DR4 codon 441 status could be potentially useful predictors of **TRAIL** sensitivity, and (b) doxorubicin, in **combination** with **TRAIL** , may effectively promote caspase activation in **TRAIL**-resistant tumors.

Molecular determinants of response to **TRAIL** in killing of normal and **cancer** cells.

Feb **2000**,

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17/3,K,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


10598113 PMID: 10706092

Increased death receptor 5 expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with **tumor necrosis** factor-related apoptosis-inducing ligand in vitro and in vivo.

Nagane M; Pan G; Weddle J J; Dixit V M; Cavenee W K; Huang H J
Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla 92093-0660, USA. mnagane@ucsd.edu

Cancer research (UNITED STATES) Feb 15 **2000**, 60 (4) p847-53, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The intractability of **malignant** gliomas to multimodality treatments plays a large part in their extremely poor prognosis. **Tumor necrosis** factor-related apoptosis-inducing ligand (**TRAIL**) is a novel member of the **tumor necrosis** factor (TNF) family that induces apoptosis preferentially in **tumor** cells through binding to its cognate death receptors, DR4 and DR5. Here we show that the DNA-damaging chemotherapeutic drugs, cis-diamminedichloroplatinum(II) (CDDP) and etoposide, elicited increased expression of DR5 in human glioma cells. Exposure of such cells in vitro to soluble human **TRAIL** in **combination** with CDDP or etoposide resulted in synergistic cell death that could be blocked by soluble **TRAIL**-neutralizing DR5-Fc or the caspase inhibitors, Z-Asp-CH2-DCB and CrmA. Moreover, systemic in vivo administration of **TRAIL** with CDDP synergistically suppressed both **tumor** formation and growth of established s.c. human glioblastoma xenografts in nude mice by inducing apoptosis without causing significant general toxicity. The **combination** treatment resulted in complete and durable remission in 29% of mice with the established s.c. xenografts and also significantly extended the survival of mice bearing intracerebral xenografts. These results provide preclinical proof-of-principle for a novel therapeutic strategy in which the death ligand, **TRAIL**, is safely **combined** with conventional DNA-damaging chemotherapy.

Increased death receptor 5 expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with **tumor necrosis** factor-related apoptosis-inducing ligand in vitro and in vivo.
Feb 15 **2000**,

The intractability of **malignant** gliomas to multimodality treatments plays a large part in their extremely poor prognosis. **Tumor necrosis** factor-related apoptosis-inducing ligand (**TRAIL**) is a novel member of the **tumor necrosis** factor (TNF) family that induces apoptosis preferentially in **tumor** cells through binding to its cognate death receptors, DR4 and DR5. Here we show that...

...of DR5 in human glioma cells. Exposure of such cells in vitro to soluble human **TRAIL** in **combination** with CDDP or etoposide resulted in synergistic cell death that could be blocked by soluble **TRAIL** -neutralizing DR5-Fc or the caspase inhibitors, Z-Asp-CH2-DCB and CrmA. Moreover, systemic in vivo administration of **TRAIL** with CDDP synergistically suppressed both **tumor** formation and growth of established s.c. human glioblastoma xenografts in nude mice by inducing apoptosis without causing significant general toxicity. The **combination** treatment resulted in complete and durable remission in 29% of mice with the established s...

... provide preclinical proof-of-principle for a novel therapeutic strategy in which the death ligand, **TRAIL**, is safely **combined** with conventional DNA-damaging chemotherapy.

Descriptors: Antineoplastic Agents--pharmacology--PD; *Glioma --drug therapy--DT; *Membrane Glycoproteins--pharmacology--PD; *Receptors, **Tumor Necrosis** Factor--biosynthesis--BI; ***Tumor Necrosis** Factor--pharmacology--PD...; pathology--PA; Mice; Mice, Inbred BALB C; Neoplasm Transplantation; Protein p53--physiology--PH; Transplantation, Heterologous; **Tumor** Cells, Cultured

Chemical Name: Antineoplastic Agents; Membrane Glycoproteins; Protein p53 ; Receptors, **Tumor Necrosis** Factor; TNF-related apoptosis-inducing ligand; **Tumor Necrosis** Factor; death receptor-5; Cisplatin; DNA

17/3,K,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


10585180 PMID: 10690508

Molecular determinants of response to **TRAIL** in killing of normal and **cancer** cells.

Kim K; Fisher M J; Xu S Q; el-Deiry W S

Howard Hughes Medical Institute, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.

Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Feb **2000**, 6 (2) p335-46, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA75138-01; CA; NCI; CA75454-01; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The **tumor necrosis** factor-related apoptosis-inducing ligand ( **TRAIL** or Apo2L) is a potent inducer of death of **cancer** but not normal cells, which suggests its potential use as a **tumor**-specific antineoplastic agent. **TRAIL** binds to the proapoptotic death receptors DR4 and the p53-regulated proapoptotic KILLER/DR5 as well as to the decoy receptors TRID and TRUNDD. In the present studies, we identified a subgroup of **TRAIL**-resistant **cancer** cell lines characterized by low or absent basal DR4 or high expression of the caspase activation inhibitor FLIP. Four of five **TRAIL**-sensitive cell lines expressed high levels of DR4 mRNA and protein, whereas six of six **TRAIL**-resistant cell lines expressed low or undetectable levels of DR4 (chi 2; P < 0.01). FLIP

17/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


10695400 PMID: 10810622
KILLER/DR5, a novel DNA-damage inducible death receptor gene, links the p53-**tumor** suppressor to caspase activation and apoptotic death.
Wu G S; Kim K; el-Deiry W S
Howard Hughes Medical Institute, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
Advances in experimental medicine and biology (UNITED STATES) **2000**, 465 p143-51, ISSN 0065-2598 Journal Code: 0121103
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
**TRAIL** and its emerging receptors are the newest members of the TNF receptor super-family. The activation of **TRAIL** receptors by ligand binding leads to apoptosis through caspase activation through an as yet unclear signaling pathway that does not require the FADD adaptor. The **TRAIL** receptor KILLER/DR5, is induced by DNA damage and appears to be regulated by the **tumor** suppressor gene p53. Both the Fas receptor and KILLER/DR5 provide potential links between DNA damage-mediated activation of the p53 **tumor** suppressor and caspase activation. While further evaluation of the role of **TRAIL** receptors in human **cancer** is ongoing, initial studies suggest that both KILLER/DR5 and DR4 may be targets for inactivation and that these pro-apooptotic receptors may be **tumor** suppressor genes. Understanding the regulation of **TRAIL** and its receptors may thus be beneficial for the development of novel approaches for **cancer** treatment.. **TRAIL** appears to be a **cancer** -specific cytotoxic agent and thus offers promise as a novel therapy for **cancer** either through replacement of the cytokine or potentially via gene replacement. Preliminary studies suggest the potential to **combine** **TRAIL** with classical cytotoxic chemotherapeutic drugs to achieve synergistic cell killing.

KILLER/DR5, a novel DNA-damage inducible death receptor gene, links the p53-**tumor** suppressor to caspase activation and apoptotic death.
**2000**,
**TRAIL** and its emerging receptors are the newest members of the TNF receptor super-family. The activation of **TRAIL** receptors by ligand binding leads to apoptosis through caspase activation through an as yet unclear signaling pathway that does not require the FADD adaptor. The **TRAIL** receptor KILLER/DR5, is induced by DNA damage and appears to be regulated by the **tumor** suppressor gene p53. Both the Fas receptor and KILLER/DR5 provide potential links between DNA damage-mediated activation of the p53 **tumor** suppressor and caspase activation. While further evaluation of the role of **TRAIL** receptors in human **cancer** is ongoing, initial studies suggest that both KILLER/DR5 and DR4 may be targets for inactivation and that these pro-apooptotic receptors may be **tumor** suppressor genes. Understanding the regulation of **TRAIL** and its receptors may thus be beneficial for the development of novel approaches for **cancer** treatment. **TRAIL** appears to be a **cancer** -specific cytotoxic agent and thus offers promise as a novel therapy for **cancer** either through replacement of the cytokine or potentially via gene replacement. Preliminary studies suggest the potential to **combine** **TRAIL** with classical cytotoxic chemotherapeutic drugs to achieve synergistic cell killing.
Descriptors: Apoptosis; *Caspases--metabolism--ME; *DNA Damage; *Linkage (Genetics); *Protein p53--genetics--GE; *Receptors, **Tumor** **Necrosis** Factor--genetics--GE; Animals; Enzyme Activation; Gene Therapy; Ligands; Neoplasms--therapy--TH; Receptors, **Tumor** **Necrosis** Factor--physiology--PH
Chemical Name: Ligands; Protein p53; Receptors, **Tumor**

**Necrosis** Factor; death receptor-5; Caspases

17/3,K,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)


10598113 PMID: 10706092
Increased death receptor 5 expression by chemotherapeutic agents in human

Implication of multiple mechanisms in apoptosis induced by the synthetic retinoid CD437 in human prostate carcinoma cells.

Sun S Y; Yue P; Lotan R

Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, TX 77030, USA.

Oncogene (ENGLAND) Sep 14 **2000**, 19 (39) p4513-22, ISSN 0950-9232 Journal Code: 8711562

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The synthetic retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) induces apoptosis in several types of **cancer** cell. CD437 inhibited the growth of both androgen-dependent and -independent human prostate carcinoma (HPC) cells in a concentration-dependent manner by rapid induction of apoptosis. CD437 was more effective in killing androgen-independent HPC cells such as DU145 and PC-3 than the androgen-dependent LNCaP cells. The caspase inhibitors Z-VAD-FMK and Z-DEVD-FMK blocked apoptosis induced by CD437 in DU145 and LNCaP cells, in which increased caspase-3 activity and PARP cleavage were observed, but not in PC-3 cells, in which CD437 did not induce caspase-3 activation and PARP cleavage. Thus, CD437 can induce either caspase-dependent or caspase-independent apoptosis in HPC cells. CD437 increased the expression of c-Myc, c-Jun, c-Fos, and death receptors DR4, DR5 and Fas. CD437's potency in apoptosis induction in the different cell lines was correlated with its effects on the expression of oncogenes and death receptors, thus implicating these genes in CD437-induced apoptosis in HPC cells. However, the importance and contribution of each of these genes in different HPC cell lines may vary. Because CD437 induced the expression of DR4, DR5 and Fas, we examined the effects of **combining** CD437 and **tumor necrosis** factor (TNF)-related apoptosis-inducing ligand ( **TRAIL** ) and Fas ligand, respectively, in HPC cells. We fo

11118476 PMID: 11156424

Augmentation of **tumor necrosis** factor-related apoptosis-inducing ligand (**TRAIL**)-induced apoptosis by the synthetic retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) through up-regulation of **TRAIL** receptors in human lung **cancer** cells.

Sun S Y; Yue P; Hong W K; Lotan R

Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA. ssun@mdanderson.org

Cancer research (United States) Dec 15 **2000**, 60 (24) p7149-55, ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: U19 CA68437; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

**Tumor necrosis** factor-related apoptosis-inducing ligand ( **TRAIL** ) induces apoptosis via the death receptors DR4 and DR5 in different transformed cells in vitro and exhibits potent antitumor activity in vivo with minor side effects. The synthetic retinoid CD437 is a potent inducer of apoptosis in **cancer** cells through increased levels of death receptors. We demonstrate that treatment of human lung **cancer** cells with a **combination** of suboptimal concentrations of CD437 and **TRAIL** enhanced induction of apoptosis in **tumor** cell lines with wild-type p53 but not in normal lung epithelial cells. CD437 up-regulated DR4 and DR5 expression. The CD437 and **TRAIL combination** enhanced activation of caspase-3, caspase-7, caspase-8, and caspase-9 and the subsequent cleavage of poly(ADP-ribose) polymerase and DNA fragmentation factor 45. Caspase inhibitors blocked the induction of apoptosis by this **combination**. Moreover, this **combination** induced Bid cleavage and increased cytochrome c release from mitochondria. These results suggest that the mechanism of enhanced apoptosis by this **combination** involves p53-dependent increase of death receptors by CD437, activation of these receptors by **TRAIL**, enhanced Bid cleavage, release of cytochrome c, and activation of caspase-3, caspase-7, caspase-8, and caspase-9. These findings suggest a novel strategy for the prevention and treatment of human lung **cancer** with the CD437 and **TRAIL combination**.

Augmentation of **tumor necrosis** factor-related apoptosis-inducing ligand (**TRAIL**)-induced apoptosis by the synthetic retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) through up-regulation of **TRAIL** receptors in human lung **cancer** cells.

Dec 15 **2000**,

**Tumor necrosis** factor-related apoptosis-inducing ligand ( **TRAIL** ) induces apoptosis via the death receptors DR4 and DR5 in different transformed cells in vitro...

... with minor side effects. The synthetic retinoid CD437 is a potent inducer of apoptosis in **cancer** cells through increased levels of death receptors. We demonstrate that treatment of human lung **cancer** cells with a **combination** of suboptimal concentrations of CD437 and **TRAIL** enhanced induction of apoptosis in **tumor** cell lines with wild-type p53 but not in normal lung epithelial cells. CD437 up-regulated DR4 and DR5 expression. The CD437 and **TRAIL combination** enhanced activation of caspase-3, caspase-7, caspase-8, and caspase-9 and the subsequent...

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apoptosis by this **combination** involves p53-dependent increase of death receptors by CD437, activation of these receptors by **TRAIL**, enhanced Bid cleavage, release of cytochrome c, and activation of caspase-3, caspase-7, caspase...

... 9. These findings suggest a novel strategy for the prevention and treatment of human lung **cancer** with the CD437 and **TRAIL** **combination**.

Descriptors: Apoptosis--drug effects--DE; *Lung Neoplasms--pathology--PA; *Membrane Glycoproteins--metabolism--ME; *Receptors, **Tumor** **Necrosis** Factor--metabolism--ME; *Retinoids--pharmacology--PD; * **Tumor** **Necrosis** Factor--metabolism--ME; *Up-Regulation...; ME; Poly(ADP-ribose) Polymerases--metabolism--ME; Proto-Oncogene Proteins c-bcl-2--metabolism--ME; **Tumor** Cells, Cultured

11150687 PMID: 11212300

Chemotherapy and immunotherapy of **malignant** glioma: molecular mechanisms and clinical perspectives.

Roth W; Weller M

Department of Neurology, University of Tubingen, School of Medicine, Germany.

Cellular and molecular life sciences - CMLS (Switzerland) Oct 30 **1999**, 56 (5-6) p481-506, ISSN 1420-682X Journal Code: 9705402

Document type: Journal Article; Review; Review, Academic

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Despite the considerable progress in modern **tumor** therapy, the prognosis for patients with glioblastoma, the most frequent **malignant** brain **tumor** , has not been substantially improved. Although cytoreductive surgery and radiotherapy are the mainstays of treatment for **malignant** glioma at present, novel cytotoxic drugs and immunotherapeutic approaches hold great promise as effective weapons against these **malignancies** . Thus, great efforts are being made to enhance antitumoral efficacy by **combining** various cytotoxic agents, by novel routes of drug administration, or by **combining** anticancer drugs and immune modulators. Immunotherapeutic approaches include cytotoxic cytokines, targeted antibodies, and vaccination strategies. However, the success of most of these experimental therapies is prevented by the marked molecular resistance of glioma cells to diverse cytotoxic agents or by glioma-associated immunosuppression. One promising experimental strategy to target glioma is the employment of death ligands such as CD95 (Fas/Apo1) ligand or Apo2 ligand (**TRAIL**). Specific proapoptotic approaches may overcome many of the obvious obstacles to a satisfactory management of **malignant** brain tumors.

```
? ds

Set      Items   Description
S1       13644   TRAIL
S2        1710   ANTIPROGESTIN
S3           7   S1 AND S2
S4           3   RD (unique items)
S5     2703994   CANCER OR TUMOR OR MALIGNAN?
S6        4182   S1 AND S5
S7     2481799   COMBIN?
S8         772   S6 AND S7
S9         230   S8 AND PY<=2001
S10        126   S9 AND PY<2001
? s necrosis
     S11  406282  NECROSIS
? s s10 and s11
              126  S10
           406282  S11
     S12       69  S10 AND S11
? s cancer or malignan?
          1389109  CANCER
           551948  MALIGNAN?
     S13 1788350  CANCER OR MALIGNAN?
? s s12 not s5
              69  S12
         2703994  S5
     S14       0  S12 NOT S5
? s s12 and s13
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         1788350  S13
     S15      40  S12 AND S13
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>>>Duplicate detection is not supported for File 340.

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Processing
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        42132857  PY<=2001
     S17      20  S16 AND PY<=2001
? t s17/3,k,ab/1-20

 17/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

14498199   PMID: 10493964
   Selectivity of TRAIL-mediated apoptosis of cancer cells and
synergy with drugs: the trail to non-toxic cancer therapeutics
(review).
  Bonavida B; Ng C P; Jazirehi A; Schiller G; Mizutani Y
  Department of Microbiology and Immunology, UCLA School of Medicine, Los
Angeles, CA 90095-1747, USA.
  International journal of oncology (GREECE) Oct 1999, 15 (4)
 p793-802, ISSN 1019-6439 Journal Code: 9306042
  Document type: Journal Article; Review; Review, Tutorial
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  There have been many advances in the therapy of cancer following
the introduction of cytotoxic chemotherapeutic drugs. Notable responses
were observed in primary tumors and often in malignant metastatic
```

tumors. However, one of the consequences of chemotherapy is the development/acquisition of drug-resistant phenotypes and the development of multiple drug resistance. The development of drug resistance remains a major obstacle in the treatment of such tumors and therefore, there is an obvious need for alternative approaches such as immune/gene therapy. The cloning of biologically active cytotoxic molecules has been considered as potential new therapeutics in the destruction of drug-resistant **tumor** cells. For instance, some members of the TNF-superfamily are characterized by their ability to inflict cell death upon binding to their cognate receptors. TNF-alpha was the first molecule to be tested for its anti-**tumor** activity, followed by Fas-ligand. These two molecules are efficient in killing a variety of **tumor** cells, however, they cause significant damage to normal tissues that result in life-threatening toxicities. Therefore, the search for a cytotoxic molecule that is selective for **tumor** cells has continued until the recently discovered new member of the TNF superfamily, namely **TRAIL**/APO-2L. **TRAIL** has been shown to be selectively cytotoxic in inducing apoptosis against **tumor** cells and has minimal or no toxicity against normal tissues, as examined both in vitro and in vivo in mice. Therefore, **TRAIL** is a new agent that has great potential for its in vivo anti-**cancer** effect, whether used alone or in **combination** with drugs. Studies from our laboratory have recently demonstrated that **tumor** cells that are resistant to **TRAIL** can be sensitized by subtoxic concentrations of drugs/cytokines and the sensitized **tumor** cells are significantly killed by **TRAIL**. This review describes the current status of research studies performed with **TRAIL** by other investigators as well as by our laboratory.

Selectivity of **TRAIL**-mediated apoptosis of **cancer** cells and synergy with drugs: the **trail** to non-toxic **cancer** therapeutics (review).

Oct **1999**,

There have been many advances in the therapy of **cancer** following the introduction of cytotoxic chemotherapeutic drugs. Notable responses were observed in primary tumors and often in **malignant** metastatic tumors. However, one of the consequences of chemotherapy is the development/acquisition of drug...

...cytotoxic molecules has been considered as potential new therapeutics in the destruction of drug-resistant **tumor** cells. For instance, some members of the TNF-superfamily are characterized by their ability to...

... their cognate receptors. TNF-alpha was the first molecule to be tested for its anti-**tumor** activity, followed by Fas-ligand. These two molecules are efficient in killing a variety of **tumor** cells, however, they cause significant damage to normal tissues that result in life-threatening toxicities. Therefore, the search for a cytotoxic molecule that is selective for **tumor** cells has continued until the recently discovered new member of the TNF superfamily, namely **TRAIL**/APO-2L. **TRAIL** has been shown to be selectively cytotoxic in inducing apoptosis against **tumor** cells and has minimal or no toxicity against normal tissues, as examined both in vitro and in vivo in mice. Therefore, **TRAIL** is a new agent that has great potential for its in vivo anti-**cancer** effect, whether used alone or in **combination** with drugs. Studies from our laboratory have recently demonstrated that **tumor** cells that are resistant to **TRAIL** can be sensitized by subtoxic concentrations of drugs/cytokines and the sensitized **tumor** cells are significantly killed by **TRAIL** . This review describes the current status of research studies performed with **TRAIL** by other investigators as well as by our laboratory.

...Descriptors: Drug Toxicity--prevention and control--PC; *Membrane Glycoproteins--therapeutic use--TU; *Neoplasms--drug therapy--DT; * **Tumor Necrosis** Factor--therapeutic use--TU; Animals; Drug Screening Assays, Antitumor; Drug Synergism; Mice; Multigene Family --physiology--PH; Sensitivity and Specificity; **Tumor** Cells, Cultured;

```
      ---  -----  -----------
? s mifepristone
      S1    6570  MIFEPRISTONE
? s death(w)receptor??
          620110  DEATH
         2173312  RECEPTOR??
      S2    5196  DEATH(W)RECEPTOR??
? s s1 and s2
            6570  S1
            5196  S2
      S3      10  S1 AND S2
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...completed examining records
      S4       7  RD (unique items)
? t s4/3,k,ab/1-7

 4/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2004 The Dialog Corp. All rts. reserv.

12412586   PMID: 12810637
  Glucocorticoid  cotreatment  induces  apoptosis  resistance toward cancer
therapy in carcinomas.
```

```
? s antiprogestin
      S5     1710  ANTIPROGESTIN
? s death(w)receptor
          620110  DEATH
         1728112  RECEPTOR
      S6     3964  DEATH(W)RECEPTOR
? s s5 and s6
            1710  S5
            3964  S6
      S7        3  S5 AND S6
? rd
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? t s8/3,k,ab/1-3

 8/3,K,AB/1      (Item 1 from file: 155)
```

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      ---  -----  -----------
? s mifepristone or onapristone
            6570  MIFEPRISTONE
             545  ONAPRISTONE
      S1    6859  MIFEPRISTONE OR ONAPRISTONE
? s dr5 or dr(w)5 or dr4 or dr(w)4
Processing
            2579  DR5
           99464  DR
         8422856  5
             247  DR(W)5
            8280  DR4
           99464  DR
         8359714  4
             396  DR(W)4
      S2   10257  DR5 OR DR(W)5 OR DR4 OR DR(W)4
? s s1 and s2
            6859  S1
           10257  S2
      S3       2  S1 AND S2
? rd
>>>Duplicate detection is not supported for File 340.
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11/3,K,AB/3 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci


08523530 Genuine Article#: 296AR Number of References: 45
Title: Induction of apoptosis by **mifepristone** and tamoxifen in human **LNCaP prostate** cancer cells in culture (ABSTRACT AVAILABLE )
Author(s): ElEtreby MF (REPRINT) ; Liang YY; Lewis RW
Corporate Source: MED COLL GEORGIA,DEPT SURG, UROL SECT, BAA-8414/AUGUSTA//GA/30912 (REPRINT)
Journal: PROSTATE, **2000**, V43, N1 (APR 1), P31-42
ISSN: 0270-4137 Publication date: 20000401
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012
Language: English Document Type: ARTICLE
Abstract: BACKGROUND. Published data indicate that antiprogestins and antiestrogens could inhibit **prostate** cancer cell growth in vitro and in vivo. The main objective of the present studies was to explore the role of bcl(2) and TGF beta(1) for induction of apoptosis in **LNCaP prostate** cancer cells growing in culture as a treatment response to the antiprogestin, **mifepristone**, and the antiestrogen, 4-hydroxytamoxifen.

METHODS. In vitro cell viability (cytotoxicity), DNA fragmentation, and changes in the expression of bcl(2) and TGF beta(1) proteins were assessed using the sulforhodamine B protein dye-binding assay, specific ELISA, and competitive inhibition assays.

RESULTS. Both steroid antagonists induced a significant time- and dose-dependent cell growth inhibition (cytotoxicity). This inhibition of viable cells was associated with a significant **increase** in DNA fragmentation (apoptosis), downregulation of bcl(2), and induction of TGF beta(1), protein. Abrogation of the **mifepristone**- and 4-hydroxytamoxifen-induced cytotoxicity by TGF beta(1)-neutralizing antibody and by the addition of mannose-6-phosphate confirmed the correlation between induction of active TGF beta(1) and subsequent **prostate** cancer cell death. The effect of **mifepristone** was not significantly reduced or prevented by occupying the progesterone or glucocorticoid receptors by their corresponding high-affinity native ligands. On the contrary, the effect of a combination of **mifepristone** with progesterone or hydrocortisone on the **increase** in DNA fragmentation, bcl(2) downregulation, and induction of TGF beta(1) protein was additive and significantly different ($P < 0.05$) from the effect of **mifepristone** monotherapy.

CONCLUSIONS. Our data suggest that **mifepristone** and tamoxifen are effective inducers of apoptosis and may represent nonandrogen-ablation, novel therapeutic approaches to over-come a potential intrinsic apoptosis resistance of androgen-independent **prostate** cancer cells. **Prostate** 43:31-42, 2000. (C) 2000 Wiley-Liss, Inc.

Title: Induction of apoptosis by **mifepristone** and tamoxifen in human **LNCaP prostate** cancer cells in culture
, **2000**
Abstract: BACKGROUND. Published data indicate that antiprogestins and antiestrogens could inhibit **prostate** cancer cell growth in vitro and in vivo. The main objective of the present studies...

...explore the role of bcl(2) and TGF beta(1) for induction of apoptosis in **LNCaP prostate** cancer cells growing in culture as a treatment response to the antiprogestin, **mifepristone**, and the antiestrogen, 4-hydroxytamoxifen.

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CONCLUSIONS. Our data suggest that **mifepristone** and tamoxifen are effective inducers of apoptosis and may represent nonandrogen-ablation, novel therapeutic approaches to over-come a potential intrinsic apoptosis resistance of androgen-independent **prostate** cancer cells. **Prostate** 43:31-42, 2000. (C) 2000 Wiley-Liss, Inc.

...Identifiers--GROWTH-FACTOR-BETA; PROTEIN-KINASE-C; ANTITUMOR-ACTIVITY; ESTROGEN-**RECEPTOR**; TRANSFORMING GROWTH-FACTOR-BETA-1; PROGESTERONE ANTAGONISTS; PHOSPHOLIPASE-D; IN-VITRO; ANDROGEN; RAT

11/3,K,AB/4 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci


06906614 Genuine Article#: 101EY Number of References: 132
Title: Antiprogestin pharmacodynamics, pharmacokinetics, and metabolism: Implications for their long-term use (ABSTRACT AVAILABLE)
Author(s): Jang GR; Benet LZ (REPRINT)
Corporate Source: UNIV CALIF SAN FRANCISCO,DEPT BIOPHARMACEUT SCI, 513 PARNASSUS AVE/SAN FRANCISCO//CA/94143 (REPRINT); UNIV CALIF SAN FRANCISCO,DEPT BIOPHARMACEUT SCI/SAN FRANCISCO//CA/94143
Journal: JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS, **1997**, V25 , N6 (DEC), P647-672
ISSN: 0090-466X Publication date: 19971200
Publisher: PLENUM PUBL CORP, 233 SPRING ST, NEW YORK, NY 10013
Language: English Document Type: REVIEW
Abstract: Antiprogestins represent a relatively new and promising class of therapeutic agents that could have significant impact on human health and reproduction. In the present work, the pharmacodynamics, pharmacokinetics, and metabolism of **mifepristone** (MIF), lilopristone (LIL), and onapristone (ONA) in humans are reviewed, and characteristics bearing important clinical implications are discussed. Although MIF has gained notoriety as an ''abortion pill, '' antiprogestins may more importantly prove effective in the treatment of endometriosis, uterine leiomyoma, meningioma, cancers of the breast and **prostate**, and as contraceptive agents. MIF pharmacokinetics display nonlinearities associated with saturable plasma protein (a I-acid glycoprotein, AAG) binding and characterized by lack of dose dependency for parent drug plasma concentrations (for doses greater than 100 mg) and a zero-order phase of elimination. LIL and ONA pharmacokinetics are less well characterized but ONA does not appear to

bind AAG and displays a much shorter t(1/2) than the other agents. The three antiprogestins are substrates of cytochrome P450 (CYP) 3A4, an enzyme exceedingly important in human xenobiotic metabolism. Even more implicative of likely drug-drug interactions subsequent to their long-term administration are recent data from our laboratory indicating that they inactivate CYP3A4 in a cofactor- and time-dependent manner, suggesting that complexation and induction of the enzyme may occur in vivo via protein stabilization. Moreover, it has been demonstrated that MIF **increases** CYP3A4 mRNA levels in human hepatocytes in primary culture, indicative of message stabilization and/or transcriptional activation of CYP3A4 expression. Finally, MIF has also been shown to inhibit P-glycoprotein function. Whether LIL and ONA share these latter two characteristics with MIF has not yet been determined but they illustrate properties that, in addition to diminished antiglucocorticoid activities and altered pharmacokinetic characteristics, warrant consideration during the development of these and newer antiprogestational agents.

, **1997**

...Abstract: on human health and reproduction. In the present work, the pharmacodynamics, pharmacokinetics, and metabolism of **mifepristone** (MIF), lilopristone (LIL), and onapristone (ONA) in humans are reviewed, and characteristics bearing important clinical...

...prove effective in the treatment of endometriosis, uterine leiomyoma, meningioma, cancers of the breast and **prostate**, and as contraceptive agents. MIF pharmacokinetics display nonlinearities associated with saturable plasma protein (a I...

...enzyme may occur in vivo via protein stabilization. Moreover, it has been demonstrated that MIF **increases** CYP3A4 mRNA levels in human hepatocytes in primary culture, indicative of message stabilization and/or...

...Identifiers--HUMAN PROGESTERONE-**RECEPTOR**; ORALLY ACTIVE PROSTAGLANDIN; LOW-DOSE **MIFEPRISTONE**; BREAST-CANCER-CELLS; EARLY-PREGNANCY; HUMAN-LIVER; P-GLYCOPROTEIN; MENSTRUAL-CYCLE; MAMMARY-TUMORS; POSTCOITAL CONTRACEPTION

?